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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/643,853	08/19/2003	David Y. Chien	2302-16073.10 (PP16073.02	6313

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EXAMINER	
LUCAS, ZACHARIAH	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 06/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/643,853	CHIEN ET AL.	
	Examiner	Art Unit	
	Zachariah Lucas	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *47-58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *47-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 August 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3 lists*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 47-58 are pending in the application.

Information Disclosure Statement

2. The information disclosure statements (IDS) submitted on August 19, 2003, December 17, 2004, and December 23, 2005, are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner.

Specification

3. Applicant is reminded of the proper content of an abstract of the disclosure.

A patent abstract is a concise statement of the technical disclosure of the patent and should include that which is new in the art to which the invention pertains. If the patent is of a basic nature, the entire technical disclosure may be new in the art, and the abstract should be directed to the entire disclosure. If the patent is in the nature of an improvement in an old apparatus, process, product, or composition, the abstract should include the technical disclosure of the improvement. In certain patents, particularly those for compounds and compositions, wherein the process for making and/or the use thereof are not obvious, the abstract should set forth a process for making and/or use thereof. If the new technical disclosure involves modifications or alternatives, the abstract should mention by way of example the preferred modification or alternative.

The abstract should not refer to purported merits or speculative applications of the invention and should not compare the invention with the prior art.

Where applicable, the abstract should include the following:
(1) if a machine or apparatus, its organization and operation;
(2) if an article, its method of making;
(3) if a chemical compound, its identity and use;
(4) if a mixture, its ingredients;
(5) if a process, the steps.

Extensive mechanical and design details of apparatus should not be given.

In the present case, the claims of the application are drawn to polynucleotides encoding a multiple epitope fusion antigen for use in an assay for the simultaneous detection of HCV antigens and antibodies present in a sample. This is not reflected in the abstract of the application.

Appropriate amendment of the abstract is therefore required.

4. The title of the invention is not descriptive of the claimed invention. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: Polynucleotides encoding a multiple epitope fusion antigen for use in an HCV antigen/antibody combination assay.

Claim Objections

5. Claims 47-49 are objected to because of the following informalities: the claims refer to figures in the application in the description of the claimed invention. Where possible, claims are to be complete in themselves. Incorporation by reference to a specific figure or table "is permitted only in exceptional circumstances where there is no practical way to define the invention in words and where it is more concise to incorporate by reference than duplicating a drawing or table into the claim. MPEP § 2173.05(s). It is suggested that the claims be amended to read on polynucleotides encoding the polypeptide of SEQ ID NO: 5, or polynucleotides of SEQ ID NO: 4 instead of referring to the Figures of the application. .

Appropriate correction is required.

Claim Rejections - 35 USC § 101

6. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

7. Claims 53-58 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. These claim read on "A host cell" transformed with the claimed polynucleotide. While it is recognized that the claimed polynucleotide is not a product of nature, the claims do read on human beings, whose cells have been transformed with the vector. It is suggested that the claims be amended to read on - - isolated- - host cells transformed with the indicated vectors.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 49, 52, 55, and 58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims relate to polynucleotides comprising a sequence coding for the amino acid sequence of Figures 5A-5F of the application. However, the only Figure 5 is a single figure (i.e. it is not divided into figures 5A-5F), and this figure describes the construction of a plasmid. The figure does not describe an amino acid sequence. It is therefore unclear what is being claimed.

10. Claims 47, 48, 50, 51, 53, 54, 56, and 57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims read on polynucleotides encoding polypeptides of comprising amino acid sequences of at least 80% identity to SEQ ID NO: 4 (the polypeptide of Figures 7A-7F) "which reacts specifically with anti-HCV antibodies." It is unclear if the claims are requiring that the antibodies react with any portion of the multiple epitope fusion antigen comprising the indicated sequence, or if the claims are requiring that the antibodies react specifically with a portion of the MEFA sequence within the sequence of SEQ ID NO: 4. Clarification is required.

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 47, 48, 50, 51, 53, 54, 56, and 57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims are drawn to a genus of polynucleotides encoding fusion proteins comprising any sequence with at least 80% or 90% identity to the fusion protein of SEQ ID NO: 5 and which are able to bind to anti-HCV antibodies.

The following quotation from section 2163 of the Manual of Patent Examination Procedure is a brief discussion of what is required in a specification to satisfy the 35 U.S.C. 112 written description requirement for a generic claim covering several distinct inventions:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus... See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.
>
> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

Thus, when a claim covers a genus of inventions, the specification must provide written description support for the entire scope of the genus. Support for a genus is generally found where the applicant has provided a number of examples sufficient so that one in the art would recognize from the specification the scope of what is being claimed.

However, even the presence of multiple species with in a claimed genus does not necessarily demonstrate possession of the genus. See, In re Smyth, 178 U.S.P.Q. 279 at 284-85 (CCPA 1973) (stating "where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus or combination claimed at a later date in the prosecution of a patent application."); and University of California v. Eli Lilly and Co., 43 USPQ2d 1398, at 1405 (Fed Cir 1997)(citing Smyth for support). Thus, in addition to the presence of descriptive elements such a species or of a function/structure association as suggested by the *Eli Lilly* decision, the case law also indicates that the level of certainty in the art

is also a factor that may be considered in determining if there is sufficient descriptive support for a claimed genus.

In the present case, the Applicant has provided various examples of potential multiple epitope fusion proteins, including certain modifications that may be made to the sequences therein without a loss to the overall ability of the protein to detect anti-HCV antibodies. See e.g., Tables 2-4 (pages 30-32). However, it is noted that the claims read on a genus comprising any protein with at least 90% or 80% identity to MEFA 12. As MEFA 12 comprises 892 residues, this genus includes embodiments wherein at up to 82 or 165 amino acids may be modified (e.g., by insertion, deletion, or substitution). Thus, these genera of inventions may include 82^19 or 165^19 potential protein sequences. However, while the claims require that the proteins are able to react with anti-HCV antibodies, there is no indication that any protein within the structural limitations of the claims would be capable of performing this function. This is because it is not known what modifications may be performed on the sequences such that the ability to react with the HCV antibodies is maintained.

It is known in the art that the modification of a single residue in a protein sequence can change the immunogenic properties of a protein. See e.g., Riffkin et al., Gene 279-83 (teaching that a single amino acid change between two proteins was sufficient to create antigenically different proteins). Further, the art also teaches more generally that the effects of amino acid substitution in a protein are unpredictable. See e.g., Bowie et al., Science 248: 1306-10, esp. page 1306. Thus, the art teaches that the effects of making changes to an amino acid sequence are unpredictable, and that such changes may, without further information than the sequence alone (e.g. essential residues), result in a change in the proteins ability to interact with a protein

specific antibody. I.e., the art teaches that absent knowledge of what residues or regions of a protein interact with immune bodies, the effects of modifying the protein's sequence will be unpredictable. I.e., the art indicates that there would be uncertainty in the art as to what modifications to the proteins may be performed such that the claimed proteins (and the epitopic regions within it) would retain the ability to bind the target HCV antibodies.

With respect to sequences other than those specifically disclosed, it is noted that the prior art teaches numerous HCV sequences, many of which presumably fall within the range of the indicated sequence identity. However, it is noted that not every sequence with 80% identity is an HCV sequence that would be recognized by anti-HCV antibodies. It is not clear from the application what structures, residues, or regions in the claimed sequences must be maintained for the compositions to induce an anti-HCV response. I.e., there has been insufficient showing to demonstrate possession of any structure that corresponds to the required functional characteristics of the claimed genus. Thus, while the teachings of the prior art and the application may provide support for compositions wherein the HCV antigens have the sequence of MEFA 12, or similar MEFA proteins comprising the corresponding regions of other HCV isolates, the application has not provided sufficient support for any sequence of at least 80% or 90% identity to MEFA 12 that would be able to react with the target antibodies.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 47, 48, 50, 51, 53, 54, 56, and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Valenzuela et al. (WO 97/44469- of record in the August 2003 IDS), in view of the teachings of Chien et al. (Vir Hepat Liver Dis pp 320-24- reference C5 in the August 2003 IDS), Puntoriero et al. (EMBO J 17: 3521-33), and Hartman et al. (U.S. 6,001,604). These claims are drawn to polynucleotides that encodes multiple epitope fusion antigens (MEFA) with 80% or 90% sequence identity to the MEFA disclosed in Figure 7 of the application (which is the same as the protein of SEQ ID NO: 5, and is encoded by the polynucleotide of SEQ ID NO: 4). This fusion antigen of Figure 7, referred to as MEFA 12 in the application, is further described by the following Table from page 30 of the specification:

Table 2. MEFA 12

mefa aa#	5' end site	epitope	hcv aa#	strain
1-69*	*Nco*I	hSOD		
72-89	*Mlu*I	E1	303-320	1
92-112	*Hind*III	E2 HVR1a consensus	390-410	1
113-143		E2 HVR1+2 consensus	384-414	1, 2
146-392	*Spe*I	C33C short	1211-1457	1
395-441	*Sph*I	5-1-1	1689-1735	1
444-490	*Nru*I	5-1-1	1689-1735	3
493-539	*Cla*I	5-1-1	1689-1735	2
542-577	*Ava*I	C100	1901-1936	1
580-615	*Xba*I	NS5	2278-2313	1
618-653	*Bgl*II	NS5	2278-2313	1
654-741	*Nco*I	core epitopes	9-53, R47L 64-88 67-84	1 1 2
742-829	*Bal*I	core epitopes	9-53, R47L 64-88 67-84	1 1 2

Because the claims read on proteins with either 80 or 90 percent identity to the sequence, the claims read on proteins with less than about 82 (for 90% identity), or less than about 165 (for 80% identity), amino acid residues that vary from the sequence of SEQ ID NO: 5.

Like the present application, Valenzuela teaches MEFA comprising various epitopes from the HCV polyprotein. The reference also provides examples of such MEFAs, including examples that comprise the antigenic regions of residues 72-89, 395-441, 444-490. 493-539, 580-615, and 618-653 of MEFA 12. Cf, Table 2 above, and Valenzuela, page 20 Table 2 (describing the contents of MEFA 6). Further, it is noted that MEFA 6 of the reference also includes a sequence corresponding to HCV residues 10-53 (representing a sequence of at least 80 or 90% identity with the 9-53 R47L sequences in the currently claimed MEFA 12), 1901-1940 (corresponding to a sequence with 80 or 90% identity to the C100 epitope of residues 542-577 of MEFA 12), and a longer version of the c33c short antigenic region of positions 146-392 of MEFA 12. It is also noted that the antigenic regions of the MEFA 6 protein have a similar organization to those of MEFA 12.

In addition to the antigenic regions disclosed as part of MEFA 6, the Valenzuela also teaches other regions that may be included in the MEFAs described therein. For example, on page 12, the reference suggests the inclusion of epitopes derived from the hypervariable region of the E2 protein spanning residues 384-410 or 390-410, including the specific sequence of the consensus sequence of residues 92-112 of the MEFA 12. Thus, it would have been obvious to those of ordinary skill in the art to modify the MEFAs described therein to include such additional sequences.

In addition to the teachings regarding the MEFA itself, the reference also teaches the recombinant production of the MEFA through use of a vector encoding it. See e.g., claim 6, and pages 2-3, 9, and 11. The reference therefore renders obvious the making and use of polynucleotides encoding the MEFAs, and recombinant vectors and cells comprising such.

However, Valenzuela does not teach or suggest the use of the shorter hSOD region used in the present MEFA (the MEFAs of Valenzuela include residues 1-154 of the hSOD sequence), the E2 sequence of residues 113-143 of MEFA 12, or the core epitopes corresponding to residues 64-88 or 67-84 of the core sequence.

Nonetheless, the use of such similar sequences to those used in MEFA 12 to result in a MEFA with at least 80 or 90% identity thereto would have been obvious to those of ordinary skill in the art.

For example, it would have been obvious to those of ordinary skill in the art that shorter stretches of the hSOD sequence would be equally useful as a leader sequence for the recombinant production of the MEFA antigen. This is demonstrated in part by the teachings of Hartman, which teaches the inclusion of only the 63 N-terminal residues (including the N-terminal Met) of a SOD protein for use as leader sequence in bacterial expression vectors. Col 10, lines 15-28.

With respect to the E2 HVR1+2 region, while Valenzuela indicates that HVR consensus sequences may be used, and teaches the HVR1 consensus used in positions 92-112 of MEFA 12, the reference does not teach what other sequences may be used. However, the reference clearly indicates that other consensus sequences derived from the HVR sequence would be useful in the described MEFAs. In addition to these teachings, the Puntoriero reference discloses a more

generic HVR consensus sequence varying from that of MEFA 12 residues 113-143 by one residue (an S→A substitution at MEFA 12 position 120). See e.g., Puntoriero, page 3522. It is noted that the MPEP indicates that it is prima facie obvious combine compositions disclosed as useful for the same purpose. MPEP § 2144.06. In the present case, Valenzuela teaches that any E2 HVR consensus sequence may be used in the MEFAs described therein, and Puntoriero discloses such a sequence. It would therefore have been obvious to those in the art to include this consensus sequence in addition to the HVR1 sequence disclosed by Valenzuela into an MEFA.

Finally, while the Valenzuela reference teaches the inclusion of a sequence comprising residues 10-53 of the HCV polyprotein, the reference does not teach or suggest the inclusion of regions corresponding to residues 64-88 or 67-84 of the core protein. However, the art indicates that such antigenic regions were known in the art, and that it was known in the art that anti-HCV serum antibodies bound to such sequences. See e.g., Chien et al., pages 322-23 (disclosing HCV core protein epitope sequences and subtype variations in this region). Thus, as the art discloses the sequences of comprising residues 67-84 as comprising sequences recognized by anti-HCV antibodies, it would have been obvious to those of ordinary skill in the art to include such sequences in the MEFA proteins of Valenzuela.

The combined teaches of these references would result in peptides varying from the peptide of MEFA 12 in: 18 spacer residues, 6 residues of the hSOD leader (69-63), one residue in the E2 HVR1+2 sequence, 19 residues in the c33c sequence, 4 residues in the C100 sequence, 4 residues in the two sequences 9-53 (representing the addition of residue 9 in MEFA 12, and the substitution of residue 47) and 14 residues (combined) in the other core epitopes (representing the addition of residues 64-66, and 85-88 two times). Thus, the MEFA suggested by the art and

MEFA 12 vary by about 66 residues, assuming that it is not obvious to include the spacers residues or the additional residues in the regions 9-53 and 64-88. Because this results in a MEFA varying from the sequence of Figure 7 (MEFA 12) by less than 82 residues, it indicates that the combined teachings of these references render obvious MEFA proteins of 90% or 80% identity to MEFA 12.

Conclusion

15. No claims are allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 571-272-0905. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Z. Lucas 6/6/06
Patent Examiner